Rule 116. The Amendment does not raise any new issues and, thus, there is no need in further search by the Examiner. The issues presented by the amended claim 6 are the same issues that are presented by the currently pending claim 6.

The Amendment was not earlier presented because the grounds for rejection were not fully appreciated until indicated in the Final Action.

By the present amendment claim 6 is amended to point out, consistent with the specification, that the solution, from which molecularly uniform hyperpolymeric hemoglobins are prepared, contains only crosslinked hperpolymeric hemoglobin molecules.

Based on the foregoing amendment and the following remarks, the application is deemed to be in condition for allowance, and Action to that end is respectfully requested.

Claim 6-8 were rejected under 35 U.S.C. § 102(b) as being anticipated by Potzschke et al. Claims 6-10 were further rejected under 35 U.S.C. §103(a) as being unpatentable over Potzschke et al. in view of Bonhard et al. It is respectfully submitted that claims 6-10 are patentable over Potzschke et al. and Bonhard et al, whether taken alone or in combination.

The Potzschke article is connected with a new artificial oxygen transporter which is stable due to the specific cross-linking method. Because the cross-linked hemoglobins are stable, they can be purified by ultrafiltration see at page 290, under "Results" where it is pointed out that: "In addition, stabilized hemoglobin hyperpolymers were well fractionable in ultrafiltration (not documented here)". That means that the Potzschke reference is not concerned with a purification of the cross-linked hemoglobin molecules by using Sephacryl S-400 gel as stated in the office action. Furthermore, from the cited paragraph "Results" at page 290 the following may be taken:

In this paragraph it is pointed out that the reaction of the hemoglobin with a specific cross-linking agent did lead to hemoglobin hyperpolymers which did not show any changes in molecular size distribution as determined by size exclusion chromatography, as can be seen in figure 1A and figures 1B. When looking at figure 1A and 1B shown at page 288, it can be seen that these figures show the original gelchromatograms of a mixture of hyperpolymers of cross-linked hemoglobin and <u>non-cross-linked hemoglobin</u> made from different incubation times (see the description of the figures beneath the figures at page 288). As can clearly be taken therefrom as well as from the respective paragraph at page 290 ("Results"), it can be seen that there is no **fractionation** of the hemoglobin cross-linked molecules but <u>only a chromatogram which shows that molecular sizes are broadly</u> distributed.

Furthermore, applicant would like to point out that at the time the cited Potzschke article was published (1992), the structure of the cross-linked hyperpolymeric hemoglobins has not yet been known, which knowledge, however, is essential for carrying out the method recited in claim 1. Furthermore, the Potzschke article does not and cannot describe separation into different molecular weight. In Potzschke article, neither fractionation of the cross-linked hemoglobin according to molecular weights with Sephacryl is described.

As it has already been pointed out the cited reference does not separate the cross-linked hemoglobin molecules with regard to their molecular weights by the aid of exclusion molecular chromatography as presently carried out with Sephacryl. The claimed method does separate the molecules of a solved compound in accordance with its hydrodynamic volume (V_n). That volume is correlated with the molecular weight (M) by the intrinsic viscosity (V_n is proportional M x $[\eta]$, η = intrinsic viscosity. Consequently, when molecular weight fractions are desired from a mixture of polymers with a broad molecular size distribution, each fraction must have similar intrinsic viscosities (of the molecules). IF this is not the case, molecules with similar molecular weight will be eluted into different molecular size fractions, although belonging to the same molecular weight fraction.

However during a cross-linking reaction with hemoglobin, compounds may be obtained which are cross-linked in a different way. The cross-linking factor however is responsible for the intrinsic viscosity of the respective molecule. With the present method, it has surprisingly been found out that such cross-linked hemoglobin compounds with specific intrinsic viscosities are separated into fractions of different molecular weights because the intrinsic viscosity of the respective molecular weight fractions are very similar. In view of the disclosure of the reference, this could not be expected since the Potzschke reference does only disclose that a cross-linking reaction between hemoglobin and specific cross-linking agents lead to stabilized hemoglobin hyperpolymers which show a broad size distribution. Since according to the Potzschke method as disclosed a separation with Sephacryl has not been obtained even with small amounts, it was highly surprising that using higher amounts of starting materials to be separated did lead to such a separation.

As to the Examiner's remark that this difference is not reflected in the present claims, it should be noted that in applicant's view the difference between the cited and the claimed method lies in the fact that according to the present method, there is indeed a separation of cross-linked hemoglobin molecules into different molecular weight fractions, whereas according to the cited reference, there is absolutely no separation of cross-linked hemoglobins into different fractions, but only an analysis

as regards the fact that the molecular size distribution of the molecules obtained by the cross-linking reactions is broad.

It is to be noted that figures A to D at page 288 of the Potzschke reference clearly show the distribution of the cross-linked molecules obtained which is shown with reference to their size exclusion volume, see also the explanations at the first paragraph of page 290 of the Potzschke reference. This clearly shows that the material obtained after the cross-linking reaction comprises a broad distribution of molecular sizes shown by the exclusion volumes of figures A to D which reflect the gelchromatograms of the method of the cited reference which in view of this result can in no case be a purification or even a separation of the molecules into different molecular weight fractions, as explained above.

As to the cited Bonhard reference, the same arguments as mentioned above can be applied. The Examiner did already point out that the Bonhard reference uses ammonium sulfate to separate noncross-linked material, i.e. the starting hemoglobin from cross-linked material since the noncross-linked hemoglobin can disintegrate into two fractions and moreover can be nephrotoxic. The Examiner has further pointed out that the motivation to combine references would not have to be the same and that the Bonhard motivation would even be the separation of such uncross-linked hemoglobin to avoid any toxicity. In view of this, it should be noted that the present method does not

comprise a separation of noncross-linked hemoglobin from cross-linked hemoglobin. According to the present method there is no noncross-linked hemoglobin in the starting material which can be separated by use of ammonium sulfate. Therefore, it is respectfully submitted the Examiner's argument of *prima facie* obviousness can not be correct since besides any similar or non-similar motivation, there is a completely different method according to the present claims at least when considering the cited Bonhard reference. Moreover, when looking through the Bonhard reference, it can be seen that in view of the known separation of non-cross-linked hemoglobin having a completely different structure from the very highly polymer hyperhemoglobins and therefore having completely different properties of their physical and chemical behaviour, it could not have been expected that an agent which is said to be capable of separating two completely different compounds, could also be used to separate compounds which are chemically and physically similar in their behaviour such as the hyperpolmer hemoglobins of different molecular weights. Insofar and contrary to the Examiner's position, one skilled in the art would not at all have had any motivation to use ammonium sulfate in particular taken into account that at the time the present invention was conceived, one of ordinary skill in the art had no knowledge about the physical behavior of then a new group of chemical compounds such as hyperpolymeric hemoglobins.

In view of the above, it is respectfully submitted that claim 6 patentably defines over the prior art and is, therefore, allowable.

Claims 7-10 depend on claim 6 and are allowable for the same reason claim 6 is allowable and further because of specific features recited therein which, when taken above and/or in combination with features recited in claim 6, are not disclosed or suggested in the prior art.

I. CONCLUSION

In view of the foregoing, it is respectfully submitted that the application is in condition for allowance, and allowance of the application is respectfully requested.

Should the Examiner require or consider it advisable that the specification, claims and/or drawings be further amended or corrected in formal respects, in order to place the case in condition for final allowance, then it is respectfully requested that such amendment or correction be carried out by Examiner's Amendment and the case passed to issue. Alternatively, should the Examiner feel that a personal discussion might be helpful in advancing this case to allowance, the Examiner is invited to

telephone the undersigned.

Respectfully submitted
for applicant,

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I hereby certify that this correspondence is being deposited with the United States Postal Service as first class mail in an envelope addressed to: Assistant Commissioner for Patents, Washington, D.C. 20231 on August 5, 1998.

David Toren